

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number    64155, 64164, 64165, 64166**

**Trade Name    Cefaclor for Oral Suspension 375mg/5ml,  
250mg/5ml, 187mg/5ml 125mg/5ml**

**Generic Name   Cefaclor for Oral Suspension 375mg/5ml,  
250mg/5ml, 187mg/5ml ,125mg/5ml**

**Sponsor Ranbaxy Pharmaceuticals, Inc.**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION 64155, 64164, 64165, 64166

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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EA/FONSI				
Pharmacology Review(s)				
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Clinical Pharmacology				
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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number    64155, 64164, 64165, 64166**

**APPROVAL LETTER**

AADA 64-155 (375 mg base/5 mL)  
64-164 (250 mg base/5 mL)  
64-165 (187 mg base/5 mL) ✓  
64-166 (125 mg base/5 mL)

OCT 2 1997

Ranbaxy Pharmaceuticals Inc.  
U.S. Agent for: Ranbaxy Laboratories Limited  
Attention: Jim Sibert  
4600 Marriott Drive  
Suite 100  
Raleigh, NC 27612

Dear Sir:

This is in reference to your abbreviated antibiotic applications dated July 7, 1995 (AADA 64-155) and September 27, 1995 (AADA 64-164, 64-165, and 64-166), submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Cefaclor for Oral Suspension, USP.

Reference is also made to your amendments dated May 28, and September 4, 1997.

We have completed the review of these abbreviated applications and have concluded that the drugs are safe and effective for use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined your Cefaclor for Oral Suspension, USP 375 mg/5 mL, 250 mg/5 mL, 187 mg/5 mL, and 125 mg/5 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ceclor® for Oral Suspension 375 mg/5 mL, 250 mg/5 mL, 187 mg/5 mL, and 125 mg/5 mL, respectively, of Eli Lilly and Company).

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require approved supplemental applications before the changes may be made.

Post-marketing reporting requirements for these abbreviated applications are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of these drugs.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

Page 2

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

*10/2/97*  
Douglas L. Sporn  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: AADA 64-155, 64-164, 64-165, 64-166  
Division File  
FIELD COPY  
HFD-610/JPhillips  
HFD-92  
HFD-210/B.Poole

Endorsements:

HFD-643/S.Rosencrance/7/30/97: updated 8/18/97  
HFD-643/J.Harrison/7/31/97  
HFD-617/M.Anderson/8/18/97  
HFD-613/A.Payne/8/18/97  
HFD-613/C.Hoppes/(final only)

X:\NEW\FIRMSNZ\LANBAXY\LTRS&REV\64155AP.F  
F/T by smr/8/18/97

APPROVAL

*8/18/97*

*8/20/97*

*8/20/97*

*9/5/97*

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      64155, 64164, 64165, 64166**

**FINAL PRINTED LABELING**

Tear along perforation

**RANBAXY**  
NDC 63304-955-43

**CEFACTOR**  
For Oral Suspension USP

**187 mg/5 mL**  
50 mL (when mixed)  
SHAKE WELL BEFORE USE

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Usual Dosage: Children: 20 mg/kg a day (40 mg/kg in stills media) in three divided doses. Adults: 250 mg three times a day. Contains Cefaclor monohydrate equivalent to 1.87 g cefaclor in a dry, pleasantly flavored mixture. Store at controlled room temperature 15° to 30° C (59° to 86° F), protected from moisture. Directions for Mixing: Add 45 mL of water in two portions to dry mixture in the bottle. Shake well after each addition. USP monohydrate equivalent to 187 mg anhydrous cefaclor. Manufactured for: Ranbaxy Pharmaceuticals, Inc. Ranbaxy, NC 27615, U.S.A. Manufactured by: Ranbaxy Laboratories Ltd. New Delhi - 110 019, India

100 mL Cefaclor for Oral Suspension, USP - 187 mg/5 mL. SHAKE WELL BEFORE USE. Over size bottle provides extra space for shaking. Store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion in 14 days.

Lot  
Exp.

Tear along perforation

**RANBAXY**  
NDC 63304-955-04

**CEFACTOR**  
For Oral Suspension USP

**187 mg/5 mL**  
100 mL (when mixed)  
SHAKE WELL BEFORE USE

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Usual Dosage: Children: 20 mg/kg a day (40 mg/kg in stills media) in three divided doses. Adults: 250 mg three times a day. See literature for complete dosage information. Contains Cefaclor monohydrate equivalent to 3.74 g cefaclor in a dry, pleasantly flavored mixture. Prior to Mixing: Store at controlled room temperature 15° to 30° C (59° to 86° F), protected from moisture. Directions for Mixing: Add 70 mL of water in two portions to dry mixture in the bottle. Shake well after each addition. Each 5 mL (Approx. one teaspoonful) will then contain Cefaclor USP monohydrate equivalent to 187 mg anhydrous cefaclor. Manufactured for: Ranbaxy Pharmaceuticals, Inc. Ranbaxy, NC 27615, U.S.A. Manufactured by: Ranbaxy Laboratories Ltd. New Delhi - 110 019, India

100 mL Cefaclor for Oral Suspension, USP - 187 mg/5 mL. SHAKE WELL BEFORE USE. Over size bottle provides extra space for shaking. Store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion in 14 days.

Lot  
Exp.

Tear along perforation

**RANBAXY**  
NDC 63304-954-01

**CEFACTOR**  
For Oral Suspension USP

**125 mg/5 mL**

**75 mL (when mixed)**  
SHAKE WELL BEFORE USE

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Tear along perforation

Usual Dosage: Children, 20 mg/kg a day (40 mg/kg in cills media) in three divided doses. Adults, 250 mg three times a day. See literature for complete dosage information.

Directions for Mixing: Add 50 mL of water in two portions to dry mixture in the bottle. Shake well after each addition. USP monohydrate equivalent to 125 mg anhydrous cefaclor.

Manufactured for: Ranbaxy Pharmaceuticals, Inc., Raleigh, NC 27612, U.S.A.

Manufactured by: Ranbaxy Laboratories Ltd., New Delhi - 110 019, India

75 mL Cefaclor for Oral Suspension, USP-125 mg/5 mL. Over size bottle provides extra space for shaking. Store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion in 14 days.

Lot: Exp:

Tear along perforation

**RANBAXY**  
NDC 63304-954-02

**CEFACTOR**  
For Oral Suspension USP

**125 mg/5 mL**

**150 mL (when mixed)**  
SHAKE WELL BEFORE USE

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Tear along perforation

Usual Dosage: Children, 20 mg/kg a day (40 mg/kg in cills media) in three divided doses. Adults, 250 mg three times a day. See literature for complete dosage information.

Directions for Mixing: Add 100 mL of water in two portions to dry mixture in the bottle. Shake well after each addition. USP monohydrate equivalent to 125 mg anhydrous cefaclor.

Manufactured for: Ranbaxy Pharmaceuticals, Inc., Raleigh, NC 27612, U.S.A.

Manufactured by: Ranbaxy Laboratories Ltd., New Delhi - 110 019, India

150 mL Cefaclor for Oral Suspension, USP-125 mg/5 mL. Over size bottle provides extra space for shaking. Store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion in 14 days.

Lot: Exp:

Tear along perforation

**RANBAXY**  
NDC 63304-956-01

**CEFACLO**  
For Oral Suspension USP

**250 mg/5 mL**  
75 mL (when mixed)  
SHAKE WELL BEFORE USE

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Tear along perforation

Usual Dosage: Children, 20 mg/kg a day (40 mg/kg in cefaclor media) in three divided doses. Adults, 250 mg three times a day. For complete dosage information, see the package insert.

Contains Cefaclor monohydrate equivalent to 250 mg cefaclor in a dry, pleasantly flavored mixture.

Prior to Mixing: Store at controlled room temperature 15° to 30° C (59° to 86° F), protected from moisture.

Directions for Mixing: Add 105 mL of water in two portions to dry mixture in the bottle. Shake well after each addition.

Each 5 mL (Approx. one teaspoonful) will then contain Cefaclor USP monohydrate equivalent to 250 mg anhydrous cefaclor.

Manufactured by: Ranbaxy Pharmaceuticals, Inc.  
Raleigh, NC 27612, U.S.A.

Manufactured by: Ranbaxy Laboratories Ltd.  
New Delhi - 110 019, India

75 mL Cefaclor for Oral Suspension, USP 250 mg/5 mL. SHAKE WELL BEFORE USE.

Over size bottle provides extra space for shaking. Store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion in 14 days.

LOT: 2 1997

Tear along perforation

**RANBAXY**  
NDC 63304-956-02

**CEFACLO**  
For Oral Suspension USP

**250 mg/5 mL**  
150 mL (when mixed)  
SHAKE WELL BEFORE USE

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Tear along perforation

Usual Dosage: Children, 20 mg/kg a day (40 mg/kg in cefaclor media) in three divided doses. Adults, 250 mg three times a day. For complete dosage information, see the package insert.

Contains Cefaclor monohydrate equivalent to 250 mg cefaclor in a dry, pleasantly flavored mixture.

Prior to Mixing: Store at controlled room temperature 15° to 30° C (59° to 86° F), protected from moisture.

Directions for Mixing: Add 105 mL of water in two portions to dry mixture in the bottle. Shake well after each addition.

Each 5 mL (Approx. one teaspoonful) will then contain Cefaclor USP monohydrate equivalent to 250 mg anhydrous cefaclor.

Manufactured by: Ranbaxy Pharmaceuticals, Inc.  
Raleigh, NC 27612, U.S.A.

Manufactured by: Ranbaxy Laboratories Ltd.  
New Delhi - 110 019, India

150 mL Cefaclor for Oral Suspension, USP 250 mg/5 mL. SHAKE WELL BEFORE USE.

Over size bottle provides extra space for shaking. Store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion in 14 days.

LOT: OCT 2 1997

Tear along perforation

**RANBAXY**  
NDC 63304-957-03

**CEFACTOR**  
For Oral Suspension USP

**375 mg/5 mL**  
50 mL (when mixed)  
SHAKE WELL BEFORE USE

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Tear along perforation

Usual Dosage: Children, 20 mg/kg a day (40 mg/kg in 2 divided doses) in three times a day. Adults, 250 mg three times a day. See literature for complete dosage information. Contains Cefactor monohydrate equivalent to 3.75 g cefactor in a dry, pleasantly flavored mixture. Prior to Mixing, store at controlled room temperature 15° to 30° C (59° to 86° F), protected from moisture. Directions for Mixing: Add 70 mL of water in two portions to dry mixture in the bottle. Shake well after each addition. Each 5 mL (Approx. one teaspoonful) will then contain Cefactor USP monohydrate equivalent to 375 mg anhydrous cefactor. USP manufactured for: Ranbaxy Pharmaceuticals, Inc. Raleigh, NC 27612, U.S.A. Manufactured by: Ranbaxy Laboratories Ltd. New Delhi - 110 019, India

50 mL Cefactor for Oral Suspension, USP-375 mg/5 mL. SHAKE WELL BEFORE USE. Over size bottle provides extra space for shaking. Store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion in 14 days.

**APPROVED**

Lot: Exp: OCT 2 1997

Tear along perforation

**RANBAXY**  
NDC 63304-957-04

**CEFACTOR**  
For Oral Suspension USP

**375 mg/5 mL**  
100 mL (when mixed)  
SHAKE WELL BEFORE USE

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Tear along perforation

Usual Dosage: Children, 20 mg/kg a day (40 mg/kg in 2 divided doses) in three times a day. Adults, 250 mg three times a day. See literature for complete dosage information. Contains Cefactor monohydrate equivalent to 7.5 g cefactor in a dry, pleasantly flavored mixture. Prior to Mixing, store at controlled room temperature 15° to 30° C (59° to 86° F), protected from moisture. Directions for Mixing: Add 70 mL of water in two portions to dry mixture in the bottle. Shake well after each addition. Each 5 mL (Approx. one teaspoonful) will then contain Cefactor USP monohydrate equivalent to 375 mg anhydrous cefactor. USP manufactured for: Ranbaxy Pharmaceuticals, Inc. Raleigh, NC 27612, U.S.A. Manufactured by: Ranbaxy Laboratories Ltd. New Delhi - 110 019, India

100 mL Cefactor for Oral Suspension, USP-375 mg/5 mL. SHAKE WELL BEFORE USE. Over size bottle provides extra space for shaking. Store in a refrigerator. May be kept for 14 days without significant loss of potency. Keep tightly closed. Discard unused portion in 14 days.

**APPROVED**

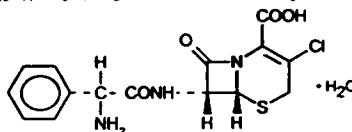
Lot: Exp: OCT 2 1997

**CEFACLOL CAPSULES USP  
and  
CEFACLOL FOR ORAL SUSPENSION USP**

**CEFACLOL CAPSULES USP  
and  
CEFACLOL FOR ORAL SUSPENSION USP**

**DESCRIPTION**

Cefaclor, USP is a semisynthetic cephalosporin antibiotic for oral administration. It is chemically designated as 3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate. The chemical formula for cefaclor is  $C_{15}H_{14}ClN_2O_5 \cdot H_2O$  and the molecular weight is 385.82.



Each capsule contains cefaclor monohydrate equivalent to 250 mg (0.68 mmol) or 500 mg (1.36 mmol) anhydrous cefaclor. The capsules also contain pregelatinized starch, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, gelatin, FD&C Blue No. 1, D&C Yellow No. 10, FD&C Red No. 40, D&C Red No. 28, titanium dioxide, sicomet black oxide and edible printing ink.

After mixing, each 5 mL of Cefaclor for Oral Suspension will contain cefaclor monohydrate equivalent to 125 mg (0.34 mmol), 187 mg (0.51 mmol), 250 mg (0.68 mmol), or 375 mg (1.0 mmol) anhydrous cefaclor. The suspensions also contain xanthan gum, sodium benzoate, sucrose, colloidal silicon dioxide, FD&C Red No. 40, flavors, sodium citrate, citric acid and simethicone emulsion.

**CLINICAL PHARMACOLOGY**

Cefaclor is well absorbed after oral administration to fasting subjects. Total absorption is the same whether the drug is given with or without food; however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed when the drug is administered to fasting subjects and generally appears from three fourths to 1 hour later. It has been reported that following administration of 250-mg, 500-mg, and 1-g doses to fasting subjects, average peak serum levels of approximately 7, 13, and 23 mcg/mL respectively were obtained within 30 to 60 minutes. Approximately 60% to 85% of the drug is excreted unchanged in the urine within 8 hours, the greater portion being excreted within the first 2 hours. During this 8-hour period, peak urine concentrations following the 250-mg, 500-mg and 1-g doses were approximately 600, 900 and 1,900 mcg/mL respectively. The serum half-life in normal subjects is 0.6 to 0.9 hour. In patients with reduced renal function, the serum half-life of cefaclor is slightly prolonged. In those with complete absence of renal function, the plasma half-life of the intact molecule is 2.3 to 2.8 hours. Excretion pathways in patients with markedly impaired renal function have not been determined. Hemodialysis shortens the half-life by 25% to 30%.

**Microbiology** - *In vitro* tests demonstrate that the bactericidal action of the cephalosporins results from inhibition of cell-wall synthesis. Cefaclor has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

**Aerobes, Gram-positive**

Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains

*Streptococcus pneumoniae*

*Streptococcus pyogenes* (group A  $\beta$ -hemolytic streptococci)

**Aerobes, Gram-negative**

*Escherichia coli*

*Haemophilus influenzae*, including  $\beta$ -lactamase-producing ampicillin-resistant strains

*Klebsiella* sp

*Proteus mirabilis*

The following *in vitro* data are available, but their clinical significance is unknown.

Cefaclor exhibits *in vitro* minimal inhibitory concentrations (MICs) of  $\leq 8$  mcg/mL or less against most ( $\geq 90\%$ ) strains of the following microorganisms; however, the safety and effectiveness of cefaclor in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

**Aerobes, Gram-negative**

*Citrobacter diversus*

*Moraxella (Branhamella) catarrhalis*

*Neisseria gonorrhoeae*

**Anaerobes, Gram-positive**

*Bacteroides* sp (excluding *Bacteroides fragilis*)

Peptococci

Peptostreptococci

*Propionibacterium acnes*

**Note:** *Pseudomonas* sp, *Acinetobacter calcoaceticus* (formerly *Mima* sp and *Herellea* sp), and most strains of enterococci (*Enterococcus faecalis* [formerly *Streptococcus faecalis*], group D streptococci), *Enterobacter* sp, indole-positive *Proteus*, and *Serratia* sp are resistant to cefaclor. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cefaclor and methicillin-type antibiotics.

**Disk Susceptibility Tests**

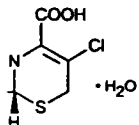
**Diffusion Techniques** - Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure<sup>1</sup> that has been recommended for use with disks to test the susceptibility of microorganisms to cefaclor uses the 30-mcg cefaclor disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefaclor. With this procedure, a report from the laboratory of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to tissues and fluids

1661 2 1997 OCT

## LES USP

## SPENSION USP

Cefaclor is a cephalosporin antibiotic chemically designated as 3-(6-oxo-4-carboxy-2-phenyl-4H-pyrimidin-5-yl)-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-1,2,4-triazine-5-carboxamide, trihydrate. Its molecular weight is 385.82.



monohydrate equivalent (1.36 mmol) anhydrous pregelatinized starch, croscarmellose sodium, magnesium stearate, D&C Yellow No. 10, titanium dioxide, and ink.

For Oral Suspension equivalent to 125 mg (0.68 mmol), or 250 mg (1.36 mmol), or 500 mg (2.72 mmol). The suspensions contain benzoyl peroxide, sucrose, No. 40, flavors, sodium emulsion.

### DOLOGY

For oral administration to children, the same whether the child is 1 year of age or older, when it is taken after meals, is 50% to 75% of the adult dose. When administered to fasting children, the average plasma concentration after three-fourths to 1 hour following administration of 250-mg tablets to fasting subjects, average plasma concentration is 7, 13, and 23 mcg/mL at 1, 2, and 3 hours, respectively. In 30 to 60 minutes, the drug is excreted in the urine. During this 8-hour period, the greater portion of the drug is excreted in the urine. Following the 250-mg dose, the plasma concentration is approximately 600, 900 and 1200 mcg/mL at 1, 2, and 3 hours, respectively. In patients with reduced renal function, the elimination half-life is slightly prolonged. In patients with renal function, the elimination half-life is 2.3 to 2.8 hours. In patients with markedly impaired renal function, hemodialysis shortens

**Microbiology** - *In vitro* tests demonstrate that the bactericidal action of the cephalosporins results from inhibition of cell-wall synthesis. Cefaclor has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

#### Aerobes, Gram-positive

Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains

*Streptococcus pneumoniae*

*Streptococcus pyogenes* (group A  $\beta$ -hemolytic streptococci)

#### Aerobes, Gram-negative

*Escherichia coli*

*Haemophilus influenzae*, including  $\beta$ -lactamase-producing ampicillin-resistant strains

*Klebsiella* sp

*Proteus mirabilis*

The following *in vitro* data are available, but their clinical significance is unknown.

Cefaclor exhibits *in vitro* minimal inhibitory concentrations (MICs) of  $\leq 8$  mcg/mL or less against most ( $\geq 90\%$ ) strains of the following microorganisms; however, the safety and effectiveness of cefaclor in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

#### Aerobes, Gram-negative

*Citrobacter diversus*

*Moraxella (Branhamella) catarrhalis*

*Neisseria gonorrhoeae*

#### Anaerobes, Gram-positive

*Bacteroides* sp (excluding *Bacteroides fragilis*)

*Peptococci*

*Peptostreptococci*

*Propionibacterium acnes*

Note: *Pseudomonas* sp, *Acinetobacter calcoaceticus* (formerly *Mima* sp and *Herellea* sp), and most strains of enterococci (*Enterococcus faecalis* [formerly *Streptococcus faecalis*], group D streptococci), *Enterobacter* sp, indole-positive *Proteus*, and *Serratia* sp are resistant to cefaclor. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cefaclor and methicillin-type antibiotics.

#### Disk Susceptibility Tests

**Diffusion Techniques** - Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure<sup>1</sup> that has been recommended for use with disks to test the susceptibility of microorganisms to cefaclor uses the 30-mcg cefaclor disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefaclor. With this procedure, a report from the laboratory of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to tissues and fluids

(eg, urine) in which high antibiotic levels can be obtained or if high dosage is used.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-mcg cefaclor disk should be interpreted according to the following criteria:

#### Zone diameter (mm)

$\geq 18$

15 - 17

$\leq 14$

#### Interpretation

Susceptible (S)

Intermediate (I)

Resistant (R)

#### When Testing *H. influenzae*\*

#### Zone diameter (mm)

$\geq 20$

17 - 19

$\leq 16$

#### Interpretation

Susceptible (S)

Intermediate (I)

Resistant (R)

\* Disk susceptibility tests performed using Haemophilus Test Medium (HTM)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 30-mcg cefaclor disk should provide the following zone diameters in these laboratory test quality control strains:

#### Microorganisms

*E. coli* ATCC 25922

*S. aureus* ATCC 25923

#### Zone Diameter (mm)

23 - 27

27 - 31

#### When Testing *H. influenzae*\*

#### Microorganisms

*H. influenzae* ATCC 49766

\* Disk susceptibility tests performed using Haemophilus Test Medium (HTM)

**Dilution Techniques** - Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds.

One such standardized procedure uses a standardized dilution method<sup>2</sup> (broth, agar, or microdilution) or equivalent with cefaclor powder. The MIC values obtained should be interpreted according to the following criteria:

#### MIC (mcg/mL)

$\leq 8$

16

$\geq 32$

#### Interpretation

Susceptible (S)

Intermediate (I)

Resistant (R)

Interpretation should be as stated above for results using diffusion techniques.

As with standard diffusion techniques, dilution methods require the use of laboratory control microorganisms. Standardized cefaclor powder should provide the following MIC values:

#### Microorganism

*E. coli* ATCC 25922

*E. faecalis* ATCC 29212

*S. aureus* ATCC 29213

#### MIC (mcg/mL)

1 - 4

$> 32$

1 - 4

#### When Testing *H. influenzae*\*

#### Microorganism

*H. influenzae* ATCC 49247

\* Broth microdilution tests performed using Haemophilus Test Medium (HTM)<sup>2</sup>

#### MIC (mcg/mL)

0.12 - 0.5

### INDICATIONS AND USAGE

Cefaclor is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

**Otitis media** caused by *S. pneumoniae*, *H. influenzae*, staphylococci, and *S. pyogenes* (group A  $\beta$ -hemolytic streptococci)

**Lower respiratory infections**, including pneumonia, caused by *S. pneumoniae*, *H. influenzae*, and *S. pyogenes* (group A  $\beta$ -hemolytic streptococci)

**Upper respiratory infections**, including pharyngitis and tonsillitis, caused by *S. pyogenes* (group A  $\beta$ -hemolytic streptococci)

Note: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefaclor is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefaclor in the subsequent prevention of rheumatic fever are not available at present.

**Urinary tract infections**, including pyelonephritis and cystitis, caused by *E. coli*, *P. mirabilis*, *Klebsiella* sp, and coagulase-negative staphylococci

**Skin and skin structure infections** caused by *Staphylococcus aureus* and *S. pyogenes* (group A  $\beta$ -hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to cefaclor.

### CONTRAINDICATIONS

Cefaclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

### WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF

THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including cefaclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

#### PRECAUTIONS

**General** - If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, eg, pressor amines, antihistamines or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cefaclor should be administered with caution in the presence of markedly impaired renal function. Since the half-life of cefaclor in anuria is 2.3 to 2.8 hours, dosage adjustments for patients with moderate or severe renal impairment are usually not required. Clinical experience with cefaclor under such conditions is limited; therefore, careful clinical observation and laboratory studies should be made.

As with other  $\beta$ -lactam antibiotics, the renal excretion of cefaclor is inhibited by probenecid.

As a result of administration of cefaclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape (Glucose Enzymatic Test Strip, USP).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

**Pregnancy** - **Pregnancy Category B** - Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given 3 times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefaclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing Mothers** - Small amounts of cefaclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/mL at 2, 3, 4, and 5 hours respectively. Trace amounts were detected at 1 hour. The effect on nursing infants is not known. Caution should be exercised when cefaclor is administered to a nursing woman.

**Pediatric Use** - Safety and effectiveness of this product for use in pediatric patients less than 1 month of age have not been established.

#### ADVERSE REACTIONS

Adverse effects considered to be related to therapy with cefaclor are listed below:

**Hypersensitivity reactions** have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' test each occur in less than 1 in 200 patients.

Cases of serum-sickness-like reactions have been reported with the use of cefaclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthritis, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. Occasionally, solitary symptoms may occur, but do not represent a serum-sickness-like reaction. While further investigation is ongoing, serum-sickness-like reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with cefaclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = 2 to 3 days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children.

Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.

More severe hypersensitivity reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylactoid events may be manifested by solitary symptoms including angioedema, asthenia, edema (including face and limbs), dyspnea, paresthesias, syncope, hypotension or vasodilatation. Anaphylaxis may be more common in patients with a history of penicillin allergy.

Rarely, hypersensitivity symptoms may persist for several months.

**Gastrointestinal symptoms** occur in about 2.5% of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Other effects considered related to therapy included eosinophilia (1 in 50 patients), genital pruritus or vaginitis (less than 1 in 100 patients), and, rarely, thrombocytopenia or reversible interstitial nephritis.

#### Causal Relationship Uncertain

**CNS** - Rarely, reversible hyperactivity, agitation, nervousness, insomnia, confusion, hypertonia, dizziness, hallucinations, and somnolence have been reported.

Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

**Hepatic** - Slight elevations of AST (SGOT), ALT (SGPT), or alkaline phosphatase values (1 in 40).

**Hematopoietic** - As has also been reported with other  $\beta$ -lactam antibiotics, transient lymphocytosis, leukopenia, and rarely, hemolytic anemia and reversible neutropenia of possible clinical significance.

There have been rare reports of increased prothrombin time with or without clinical bleeding in patients receiving cefaclor and Coumadin concomitantly.

**Renal** - Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

#### OVERDOSAGE

**Signs and Symptoms** - The toxic symptoms following an overdose of cefaclor may include nausea, vomiting, epigastric distress, and diarrhea. The severity of the epigastric distress and the diarrhea are dose related. If other symptoms are present, it is probable that they are secondary to an underlying disease state, an allergic reaction, or the effects of other intoxication.

**Treatment** - To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the

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Treatment - To obtain up-to-date information  
about the treatment of overdose, a good resource  
is your certified Regional Poison Control Center. Telephone  
numbers of certified poison control centers are listed in the

Physicians' Desk Reference (PDR). In managing  
overdosage, consider the possibility of multiple drug  
overdoses, interaction among drugs, and unusual drug  
kinetics in your patient.

Unless 5 times the normal dose of cefaclor has been  
ingested, gastrointestinal decontamination will not be  
necessary.

Protect the patient's airway and support ventilation and  
perfusion. Meticulously monitor and maintain, within  
acceptable limits, the patient's vital signs, blood gases,  
serum electrolytes, etc. Absorption of drugs from the  
gastrointestinal tract may be decreased by giving activated  
charcoal, which, in many cases, is more effective than  
emesis or lavage; consider charcoal instead of or in addition  
to gastric emptying. Repeated doses of charcoal over time  
may hasten elimination of some drugs that have been  
absorbed. Safeguard the patient's airway when employing  
gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or  
charcoal hemoperfusion have not been established as  
beneficial for an overdose of cefaclor.

#### DOSAGE AND ADMINISTRATION

Cefaclor is administered orally.

Adults - The usual adult dosage is 250 mg every 8 hours.  
For more severe infections (such as pneumonia) or  
those caused by less susceptible organisms, doses may  
be doubled.

Children - The usual recommended daily dosage for  
children is 20 mg/kg/day in divided doses every 8 hours. In  
more serious infections, otitis media, and infections caused  
by less susceptible organisms, 40 mg/kg/day are  
recommended, with a maximum dosage of 1 g/day.

Cefaclor Suspension

20 mg/kg/day

Child's Weight	125 mg/5 mL	250 mg/5 mL
9 kg	1/2 tsp t.i.d.	
18 kg	1 tsp t.i.d.	1/2 tsp t.i.d.

40 mg/kg/day

9 kg	1 tsp t.i.d.	1/2 tsp t.i.d.
18 kg		1 tsp t.i.d.

B.I.D. Treatment Option - For the treatment of otitis  
media and pharyngitis, the total daily dosage may be  
divided and administered every 12 hours.

Cefaclor Suspension

20 mg/kg/day

(Pharyngitis)

Child's Weight	187 mg/5 mL	375 mg/5 mL
9 kg	1/2 tsp b.i.d.	
18 kg	1 tsp b.i.d.	1/2 tsp b.i.d.

40 mg/kg/day

(Otitis Media)

9 kg	1 tsp b.i.d.	1/2 tsp b.i.d.
18 kg		1 tsp b.i.d.

Cefaclor may be administered in the presence of impaired  
renal function. Under such a condition, the dosage usually  
is unchanged (see PRECAUTIONS).

In the treatment of β-hemolytic streptococcal infections,  
a therapeutic dosage of cefaclor should be administered  
for at least 10 days.

#### HOW SUPPLIED

Capsules:

250 mg, blue and green, printed "RX 658" -  
(100s) NDC 63304-658-01;  
(250s) NDC 63304-658-04;  
(500s) NDC 63304-658-05;  
(unit-dose 100s) NDC 63304-658-80  
500 mg, blue and green, printed "RX 659" -  
(100s) NDC 63304-659-01;  
(250s) NDC 63304-659-04;  
(500s) NDC 63304-659-05;  
(unit-dose 100s) NDC 63304-659-80

For Oral Suspension:

125 mg/5 mL, strawberry flavor -  
(75-mL size) NDC 63304-954-01;  
(150-mL size) NDC 63304-954-02  
187 mg/5 mL, strawberry flavor -  
(50-mL size) NDC 63304-955-03;  
(100-mL size) NDC 63304-955-04  
250 mg/5 mL, strawberry flavor -  
(75-mL size) NDC 63304-956-01;  
(150-mL size) NDC 63304-956-02  
375 mg/5 mL, strawberry flavor -  
(50-mL size) NDC 63304-957-03;  
(100-mL size) NDC 63304-957-04

†After mixing, store in a refrigerator. Shake well before  
using. Keep tightly closed. The mixture may be kept for 14  
days without significant loss of potency. Discard unused  
portion after 14 days.

\*Store at controlled room temperature 15° to 30° C  
(59° to 86° F), protected from moisture.

CAUTION-Federal (USA) law prohibits dispensing without  
prescription.

#### REFERENCES

1. National Committee for Clinical Laboratory Standards,  
Performance standards for antimicrobial disk  
susceptibility tests - 5th ed., Approved Standard  
NCCLS Document M2-A5, Vol 13, No 24, NCCLS,  
Villanova, PA, 1993.
2. National Committee for Clinical Laboratory Standards,  
Methods for dilution antimicrobial susceptibility tests  
for bacteria that grow aerobically - 3rd ed., Approved  
Standard NCCLS Document M7-A3, Vol 13, No 25,  
NCCLS, Villanova, PA, 1993.

Revised : May 1997

Manufactured for :  
Ranbaxy Pharmaceuticals Inc.  
Raleigh, NC 27612, U.S.A.

Manufactured by :  
Ranbaxy Laboratories Limited  
New Delhi-110 019, India

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER 64155, 64164, 64165, 64166**

**CHEMISTRY REVIEW(S)**

OFFICE OF GENERIC DRUGS  
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO. 2
2. AADA#s 64-155, 64-164, 64-165, 64-166
3. NAME AND ADDRESS OF APPLICANT  
Ranbaxy Pharmaceuticals Inc.  
4600 Marriott Drive Suite 100  
Raleigh, North Carolina 27612
4. LEGAL BASIS FOR AADA SUBMISSION  
21 CFR §442.104b - The application is based on the RLD  
Cecclor® manufactured by Eli Lilly (AADA 62-206).
5. SUPPLEMENT(s)  
N/A
6. PROPRIETARY NAME  
N/A
7. NONPROPRIETARY NAME  
Cefaclor for Oral Suspension USP
8. SUPPLEMENT(s) PROVIDE(s) FOR  
N/A
9. AMENDMENTS AND OTHER DATES  
Firm:  
Original Submission (64-155): 7/7/95  
Amendment (64-155): 9/27/95  
Original Submission (64-164, 64-165, 64-166): 9/27/95  
Amendment (major): 5/28/97  
  
FDA:  
Refusal to File: 9/20/95  
Acknowledgement (64-165): 11/8/95  
Acknowledgement (64-155, 64-164, 64-166): 11/17/95  
Deficiency Letter: 2/7/96
10. PHARMACOLOGICAL CATEGORY  
Antibacterial
11. HOW DISPENSED  
R
12. RELATED IND/NDA/DMFs

13. DOSAGE FORM

Dry mixture for oral suspension.

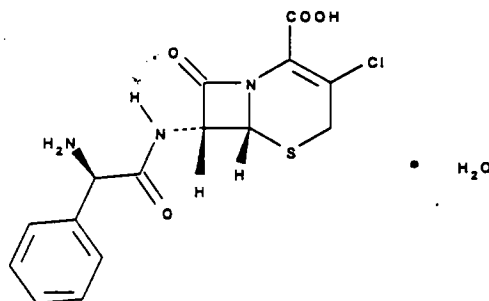
14. STRENGTH

125 mg/5 mL (64-166)

187 mg/5 mL (64-165)

250 mg/5 mL (64-164)

375 mg/5 mL (64-155)

15. CHEMICAL NAME AND STRUCTURE

3-Chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate.

C<sub>15</sub>H<sub>14</sub>ClN<sub>3</sub>O<sub>4</sub>S.H<sub>2</sub>O

Molecular Weight: 385.82

16. RECORDS AND REPORTS

N/A

17. COMMENTS

All deficiencies noted after Chemistry Review #1 were satisfactorily resolved in the firm's 5/28/97 amendment.

18. CONCLUSIONS/RECOMMENDATIONS

Approval is recommended

19. REVIEWER

Susan Rosencrance

8/18/97

DATE COMPLETED

7/30/97; updated 8/18/97

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      64155, 64164, 64165, 64166**

**BIOEQUIVALENCE REVIEW(S)**

MAY 21 1996

Dear Sir:

The Division of Bioequivalence has completed its review and has no further questions at this time.

A. SUBJ SEQ PER TRT AUCT AUCI  $C_{\text{MAX}}$   
 B. SUBJ SEQ PER TRT C1 C2 C3 .....  $C_n$

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

~~Keith K. Chan, Ph.D.~~  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

MAY 13 1996

ANDA # 64-155, 64-164, 64-165, 64-166

Cefaclor Oral Suspension

375 mg/5 mL, 250 mg/5 mL, 187 mg/5 mL, 125 mg/5 mL

Reviewer: S. P. Shrivastava

WP # 64155SDW.795

Ranbaxy Labs. Ltd.

Raleigh, NC

Submission Date:

July 7, 1995

September 27, 1995

## **REVIEW OF *IN VIVO* BIOEQUIVALENCE STUDIES AND THREE WAIVER REQUESTS**

### **I. OBJECTIVE**

The firm has submitted *in vivo* bioequivalence data on fasting and limited food studies on its cefaclor 375 mg/5 mL comparing it with Lilly's Ceclor<sup>R</sup> Oral Suspension, 375 mg/5 mL. The firm has also submitted composition data for its 375 mg/5 mL, 250 mg/5 mL, 187 mg/5 mL, and 125 mg/5 mL strength cefaclor oral suspensions for review.

### **II. BACKGROUND**

Cefaclor is a semisynthetic cephalosporin antibiotic which inhibits bacterial cell-wall synthesis in a manner similar to that of penicillin. Cefaclor is used in the treatment of otitis media, lower and upper respiratory infections, urinary tract infections and skin and skin structure infections.

Cefaclor is well absorbed after oral administration in fasting subjects. Total absorption is similar regardless whether the drug is given with or without food; however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed in fasting subjects and generally appears about 1 hour later.

Following administration of 250 mg, 500 mg, and 1 g doses in fasting subjects, average peak serum levels of approximately 7, 13, and 23  $\mu\text{g/mL}$ , respectively, were obtained within 30 to 60 minutes. Approximately 60% to 85% of the drug is excreted unchanged in urine within 8 hours, the major portion being excreted within the first 2 hours. The serum elimination half-life in subjects with normal renal function is 0.6 to 0.9 hour. In patients with complete absence of renal function, the plasma elimination half-life of the drug is 2.3 to 2.8 hours.

Currently, cefaclor is marketed by Eli Lilly under the name Ceclor<sup>R</sup>, 250 mg and 500 mg capsules, and as a powder for reconstitution as suspension for oral administration, 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL and 375 mg/5 mL. The usual adult dosage is 250 mg every 8 hours. For more severe infections (such as pneumonia), doses may be doubled.

### **III. STUDY #1. TWO-WAY CROSSOVER BIOSTUDY ON 375 MG/5 ML CEFACLOR UNDER FASTING CONDITIONS**

#### **A. Protocol #940784**

Signed and dated, Oct. 26, 1994; One Amendment dated Nov. 14, 1994.

**Laboratory/Site (Clinical):**

**Analytical Lab.**

**Investigator(s):** Principal Investigator -  
Study Physician

**IRB Approval:** Signed and dated by 10/25/94.

**Subjects:** 26 Healthy males, including 24 for the study and 2 replacements. There were no dropouts.

**Study Design:** Single-dose, two-way crossover study under fasting conditions.

**Restrictions:** Volunteers were instructed not to take any drugs including OTC drugs, one week prior to the start of the study; abstain from consuming alcohol or caffeine and/xanthine containing products 24 hours prior to and during the study.

**Inclusion/Exclusion Criteria:** Volunteers were healthy males, 18-45 years, weighing at least 60 kgs and within the 15% of ideal weight. They selected on the basis of normal observations during general physical, clinical, hematological, HIV and urinary examinations. Volunteers with history of chronic illness, e.g. alcohol or drug addiction within year; GI, renal, hepatic or cardiovascular disease; pulmonary, endocrine, immunologic, dermatologic, neurologic or psychiatric disease; subjects with abnormal clinical values, or had a history of allergic response, donated excess blood, were excluded from the study.

#### **Treatment:**

**Test Drug:** A: Ranbaxy's Cefaclor, 375 mg/5 mL suspension, Lot # P00194; Lot size: , Manuf. Date - 8/94, Exp. Date - 7/96

Other dosage levels: Same as 375 mg/5 mL suspension.

**Reference Drug:** B: Lilly's Ceclor<sup>R</sup> 375 mg/5 mL, Suspension, Lot # 8AA04A, Exp. Date 1/1/96.

**Study Dates:** 28/11/94 - 5/12/94. **Analysis Dates:** 12/16/94 - 1/18/95

**Sample Storage Period:** 51 Days

#### **B. Assay Methodology and Validation**

h

## **C. Results**

### **1. Pharmacokinetic Parameters**

- 26 subjects were used in the study. However, samples from only 24 subjects were analyzed and computed for PK parameters.
- Average pharmacokinetic parameters are given in Table 1 and Attachments 1-5.
- ANOVA analysis did not show any significant treatment, period or sequence effect on PK parameters.
- The test/reference ratios for all PK parameters (average) for the products were within 0.95-1.02 (Table 1).

- The 90% CIs for  $\text{LAUC}_{0-t}$ ,  $\text{LAUC}_{0-\infty}$ , and  $\text{LC}_{\max}$  are within the 80-125%.
- The regression coefficients for individual terminal phase of the plasma concentration-time curve were between 0.89-0.99 indicating a good curve fit, and an appropriate  $K_{el}$  and  $\text{AUC}_{0-\infty}$  estimation.
- Ratios of individual  $\text{AUC}_{0-t}/\text{AUC}_{0-\infty}$  averaged over 0.95 for the test and reference products.
- Individual PK parameters for test and reference products are given in Attachments 4-5.

**Table 1. Pharmacokinetic Parameters (%CV)**

Parameter	Test	Reference	Ratio, T/R	90% CI
$\text{AUC}_{0-T}$ , $\mu\text{g.Hr/mL}$	15.81 (15.0)	16.56 (13.3)	0.95	
$\ln \text{AUC}_{0-T}$ , $\mu\text{g.Hr/mL}$	15.65 (14.5)	16.42 (13.3)	0.95	90.6-100.4
$\text{AUC}_{0-\text{Inf}}$ , $\mu\text{g.Hr/mL}$	16.04 (15.2)	16.63 (12.4)	0.96	
$\ln \text{AUC}_{0-\text{Inf}}$ , $\mu\text{g.Hr/mL}$	15.87 (14.7)	16.50 (12.4)	0.96	91.3-101.0
$C_{\max}$ , $\mu\text{g/mL}$	16.46 (20.8)	17.16 (23.4)	0.96	
$\ln C_{\max}$ , $\mu\text{g/mL}$	16.10 (22.5)	16.67 (25.4)	0.97	88.6-105.2
$T_{\max}$ , Hr	0.49 (31.9)	0.50 (33.0)	0.98	
$T_{1/2}$ , Hr	0.624 (11.1)	0.640 (14.8)	0.98	
$K_{el}$ , $\text{Hr}^{-1}$	1.1234 (10.7)	1.1042 (13.7)	1.02	

## 2. Drug Levels in Plasma

- The plasma concentration data for all subjects are given in Table 2 and Attachment #3.
- The lower limit of quantitation, 0.2  $\mu\text{g/mL}$  was properly validated.
- The average test/reference ratios for plasma concentration during 0.25-4 hours varied between 0.89-1.01.

**TABLE 2. Mean Plasma Concentration at Each Sampling Time Point ( $\mu\text{g/mL}$ )  
(n = 24)**

TIME (HR)	TEST	CV (%)	REFERENCE	CV (%)	Ratio, T/R
Pre-dose	0.02	342	0.01	490	2.00
0.25	10.00	49	11.21	53	0.89
0.50	15.46	27	16.38	23	0.94
0.75	10.91	21	11.22	22	0.97
1.00	7.36	32	7.42	24	0.99
1.25	4.98	31	5.18	28	0.96
1.50	3.46	31	3.55	28	0.97
2.00	1.86	33	1.89	27	0.98
3.00	0.69	33	0.68	26	1.01
4.00	0.28	40	0.29	44	0.97
5.00	0.05	238	0.08	192	0.63
6.00	0.03	358	0.02	352	1.50
8.00	0.02	490	0.01	490	2.00
Ave. 0.25-4 Hours					0.97

3. **Adverse Reactions:** One case of sore throat unrelated to the test product administration was reported.

4. **Conclusion:** The fasting study is acceptable.

#### **IV. Study #2. 3-Way Crossover BE Study Under Fed and Fasted Conditions**

##### **A. Protocol # 940786**

The study site, investigators, subject selection criteria, drug products, blood sampling schedule, analytical assay, methods validation, etc. were same as in the fasting study. Certain protocol differences are indicated below.

**Subjects:** 18 Healthy male volunteers participated in the study, but two dropped out.

**Study Design:** Randomized, 3-Way crossover, 3-period, 3-sequence study.

**Drug Regimen**

- A. Ranbaxy 375 mg/5 mL cefaclor suspension administered under fasting conditions.
- B. Ranbaxy 375 mg/5 mL cefaclor suspension administered under fed conditions.
- C. Lilly's Ceclor<sup>R</sup> 375 mg/5 mL cefaclor suspension administered under fed conditions.

**Dose:** Single Oral dose, 375 mg/5 mL, administered with 240 mL water.

**Fasting/Food:** Regimen A: Subjects will be required to fast overnight before dosing and 4 hours post-dosing.  
Regimen B & C: Subject will be required to fast overnight until 30 minutes prior to their dosing time, when they will be given standard breakfast. Standard meals will be provided at 4 hours post-dosing to all subjects.

**Water:** Water will be allowed *ad libitum* except 4 hours predosing, 2 hours post-dosing, and during dosing time.

**Washout Period:** 72 Hours between dosing.

**B. Results**

**1. Pharmacokinetic Parameters**

- The firm has included Subject, Period, Residue A, Residue B, and Treatment in the ANOVA model, but it has not included Sequence as a factor. Additionally, the meaning of RESIDA AND RESIDB is not clear.
- It appears that there is no residual effect on PK parameters. However, it needs confirmation.
- Average pharmacokinetic parameters are given in Table 3 and Attachments 6-9.
- The ratios of test/reference (food) for AUCs and  $C_{max}$  are within 0.8-1.2 as required (Tables 3). However, ANOVA reanalysis with Sequence in the

model, is not provided.

- ANOVA analysis showed significant period effect on  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $T_{max}$ ,  $LAUC_{0-t}$ ,  $LAUC_{0-inf}$ , and  $LC_{max}$ .
- Individual PK parameters are given in Attachments 6-8.
- The test/reference ratios for all PK parameters for the products ranged between 0.95-1.18 (Table 3). The individual ratios ranged between 0.81-1.22, 0.8-1.2 and 0.64-1.76, respectively, for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$ .
- Food increases the  $C_{max}$  and AUCs of test product significantly.

Table 3. Pharmacokinetic Parameters ( %CV)

Parameter	Test (Fast)	Test (Food)	Reference (Food)	Ratio, T/T Fast/Food	Ratio, T/R (Food)
$AUC_{0-T}$ , $\mu\text{g.Hr/mL}$	15.10 (15.3)	13.14 (18.4)	12.60 (19.7)	1.15	1.04
$AUC_{0-inf}$ , $\mu\text{g.Hr/mL}$	15.41 (15.0)	13.48 (17.5)	13.00 (18.7)	1.14	1.04
$C_{max}$ , $\mu\text{g/mL}$	15.48 (21.8)	6.78 (27.9)	6.65 (25.3)	2.28	1.02
$T_{max}$ , Hr	0.48 (29.6)	0.92 (49.2)	0.78 (52.1)	0.52	1.18
$T_{1/2}$ , Hr	0.70 (13.3)	0.78 (11.4)	0.82 (10.6)	0.90	0.95
$K_{el}$ , $\text{Hr}^{-1}$	1.01 (13.0)	0.90 (11.2)	0.85 (11.5)	1.12	1.06
$LAUC_{0-t}$ , $\mu\text{g.Hr/mL}$	2.701	2.561	2.523	1.15	1.04
$LAUC_{0-inf}$ , $\mu\text{g.Hr/mL}$	2.721	2.589	2.555	1.14	1.03
$LC_{max}$ , $\mu\text{g/mL}$	2.685	1.908	1.871	2.17	1.04

## 2. Drug Levels in Plasma

- The plasma concentration data for all subjects are given in Table 4 and Attachment #9.

- The lower limit of quantitation, 0.2 µg/mL was properly validated.
- The average test/reference ratios for plasma concentration during 0.25-4 hours varied between 0.86-1.11.

**TABLE 4. Mean Plasma Concentration at Each Sampling Time Point (µg/mL)  
(n = 16)**

TIME (HR)	TEST (Food)	CV (%)	REFERENCE (Food)	CV (%)	Ratio, T/R (Food)
Pre-dose	0.00	----	0.00	----	----
0.25	2.85	97	3.33	66	0.86
0.50	5.39	42	5.95	39	0.91
0.75	5.79	25	5.79	27	1.00
1.00	5.45	29	5.06	20	1.08
1.25	5.03	28	4.55	19	1.11
1.50	4.92	25	4.48	23	1.10
2.00	3.59	31	3.29	25	1.09
3.00	1.72	34	1.59	34	1.08
4.00	0.67	47	0.64	40	1.05
5.00	0.22	78	0.20	86	1.10
6.00	0.02	273	0.02	273	1.00
8.00	0.00	----	0.00	----	----
Ave. 0.25-4 Hours					1.03

### 3. Adverse Reaction

Adverse reactions were not serious and no differences in the test and reference products could be detected (see Table below).

**Adverse Events****No. of Subjects**

	<u>Test (Fast)</u>	<u>Test (Fed)</u>	<u>Reference (Fed)</u>
Headache	4	0	1
Loose stools	1	0	0
Scratch in inner ear	1	0	0

4. **Conclusion:** The study requires reanalysis of data using Sequence in the ANOVA model. Study is incomplete.

**V. FORMULATION**

Comparative formulations for test and reference products, and for three other strengths of test products are given in Table 5 below. The inactive ingredients in test products are within the IIG limits. The batch size was \_\_\_\_\_ and the intended production batch size is \_\_\_\_\_. This meets the biobatch size requirement of \_\_\_\_\_ or greater.

**VI. IN VITRO RESULTS (DISSOLUTION)**

Since cefaclor is soluble in aqueous, *in vitro* dissolution of cefaclor suspension is not required.

**VII. COMMENT**

1. In future, the firm should also submit data on a computer diskette in ASCII format containing two separate files as follows:

A. SUBJ SEQ PER TRT AUCT AUCI C<sub>MAX</sub>

B. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

The fields should be delimited by one blank space, and missing values should be indicated by a period.

2. The reviewer discussed with Jim Henderson and others in the division about the residual (RES) effects and sequence (SEQ) analysis. Jim had similar issues with other drugs and had discussed with Don Schuirmann. According to Don, the test for residue, and the estimates and standard errors of treatment differences, obtained by the usual model with sequence ( $Y = \text{SEQ SUBJ(SEQ) PER TRT RES}$ ) and sponsor's model without sequence ( $Y = \text{SUBJ PER TRT RES}$ ) should be the same.

The sponsor has cited - Littell, R.C., Freund, R.J., and Spector, P.C. SAS Systems for

Linear Models, 3rd Ed., SAS Institute, Cary, NC, 1991, in support of a contrast approach to the assessment of residual effects. According to Don Schuirmann, the two contrast variables may capture the sum of squares for residuals. In the two treatment, two period standard crossover study, SEQ is included in the model because the test for SEQ is the only test we have for unequal residual effects. For a higher order crossover study (e.g. for four period, four treatment, four sequence), we have a separate test for first order residual effects. The interpretation of the SEQ test is not so clear in this case. Standard practice in CDER has been to base an assessment of residual effects on the RES test, and ignore the SEQ test for these higher order designs. Since we are going to ignore the SEQ, there is no reason to partition SUBJ into SEQ and SUBJ(SEQ). Therefore, according to Don Schuirmann, the model used by the sponsor is acceptable

#### VIII. RECOMMENDATIONS

1. The bioequivalence study conducted under fasting conditions by Ranbaxy Laboratories on its cefaclor oral suspension, 375 mg/5 mL, Lot # P00194, comparing it to Lilly's Ceclor<sup>R</sup>, 375 mg/5 mL, Lot # 8AA04A, has been found acceptable by the Division of Bioequivalence.
2. The limited food study conducted by Ranbaxy Laboratories on its cefaclor suspension, 375 mg/5 mL, Lot #P00194, comparing it to Lilly's Ceclor<sup>R</sup>, 375 mg/5 mL suspension, Lot #8AA04A, has been found acceptable by the Division of Bioequivalence. From the bioequivalence point of view, the firm has met the *in vivo* bioavailability requirements for cefaclor oral suspension, 375 mg/5 mL, and the application is acceptable.
3. The formulations for the 250 mg/5 mL, 187 mg/5 mL, and 125 mg/5 mL strengths are proportionally similar to the 375 mg/5 mL strength of the test product, which underwent bioequivalence testing. The requests for waiver of *in vivo* bioequivalence study requirements are granted as per Section 320.22(d) of Bioavailability/Bioequivalence Regulations.

The firm should be informed of comment #1 and recommendations.

S. P. Shrivastava, Ph.D.  
Division of Bioequivalence  
Review Branch II

RD INITIALED RNPatnaik  
FT INITIALED RNPatnaik

Date 5/7/96

Concur: \_\_\_\_\_ Date: 5/13/96

Keith K. Chan, Ph.D.  
Director  
Division of Bioequivalence  
Office of Generic Drugs

Attachments - 10

SPS/sps/4-6-96/64155SDW.795

cc: ANDA #64-155 , 64-164, 64-165, 64-166 (Original, Duplicate) HFD-600 (DHare), HFD-630, HFD-655 (Patnaik, Shrivastava), Drug File, Div. File.

[NOT FOR RELEASE UNDER E.O.I.]

**TABLE 5. Comparison of Reference and Test Product Formulations**  
(Amounts in mg/5 mL)

Ingredients Strength (mg/5 mL)	Test Product (mg/5 mL)			Test 375 mg/5 mL	Ref 375
	125	187	250		
Cefaclor (w/w) <sup>1</sup>	138.99	207.93	277.98	416.97	375
Xanthan Gum					
Sodium Benzoate					
Sucrose					
Colloidal Silicon Dioxide					
FD&C Red # 40					
Strawberry Flavor					
Sodium Citrate (Hydrou					
Citric Acid					
Simethicone					
Sodium Lauryl Sulfate					
Cellulose					
Corn Starch					
Silicone					

\* Listed as ingredient without potency or purity information.

<sup>1</sup> The amount is based on anhydrous base with 4.67% water content (actual), and 6% overage.

13-02-1995

10:35

Table 1  
Project No: 940784  
Summary of Results - Cefactor in Plasma  
Pharmacokinetic Parameters  
(N = 24)

	ln AUC 0-t*	ln AUCinf*	ln Cmax*	tmax	kel	Half-life
	(mcg·h/mL)	(mcg·h/mL)	(mcg/mL)	(h)	(1/h)	(h)
Ranbaxy (A)						
Mean	15.654	15.871	16.09722	0.490	1.1234	0.6240
CV	14.5	14.7	22.5	31.9	10.7	11.1
n	24	23	24	24	23	23
Lilly (B)						
Mean	16.420	16.508	16.67281	0.500	1.1042	0.6400
CV	13.3	12.4	25.4	33.0	13.7	14.8
n	24	23	24	24	23	23
Least-Squares Means						
Ranbaxy (A)	15.654	15.870	16.09722			
Lilly (B)	16.420	16.528	16.67281			
Ratio of Least-Squares Means <sup>+</sup> (A/B)%	95.3	96.0	96.5			
90% Confidence Intervals (A/B)%						
lower limit:	90.6%	91.2%	88.6%			
upper limit:	100.4%	101.1%	105.2%			
p-Value (ANOVA)						
A vs B	0.1240	0.1911	0.4898			
Period	0.2139	0.3465	0.4598			
Sequence	0.4626	0.5900	0.4404			

\* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.  
See statistics report for details on calculation of parameters.

Note: AUCinf, kel and t½ could not be estimated for Subject No. 17.

Attachment 1

000069

13-02-1995

10:37

Table 2  
Project No: 940784  
Summary of Results - Cefaclor in Plasma  
Pharmacokinetic Parameters  
(N = 24)

	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	Cmax (mcg/mL)
Ranbaxy (A)			
Mean	15.81	16.04	16.4613
CV	15.0	15.2	20.8
n	24	23	24
Lilly (B)			
Mean	16.56	16.63	17.1563
CV	13.3	12.4	23.4
n	24	23	24
Least-Squares Means			
Ranbaxy (A)	15.81	16.03	16.4613
Lilly (B)	16.56	16.65	17.1563
Ratio of Least-Squares Means (A/B)%	95.5	96.3	95.9
90% Confidence Intervals (A/B)%			
lower limit:	90.3%	91.1%	87.6%
upper limit:	100.7%	101.5%	104.3%
P-value (ANOVA)			
A vs B	0.1505	0.2361	0.4123
Period	0.1690	0.2895	0.3717
Sequence	0.5134	0.6529	0.4226

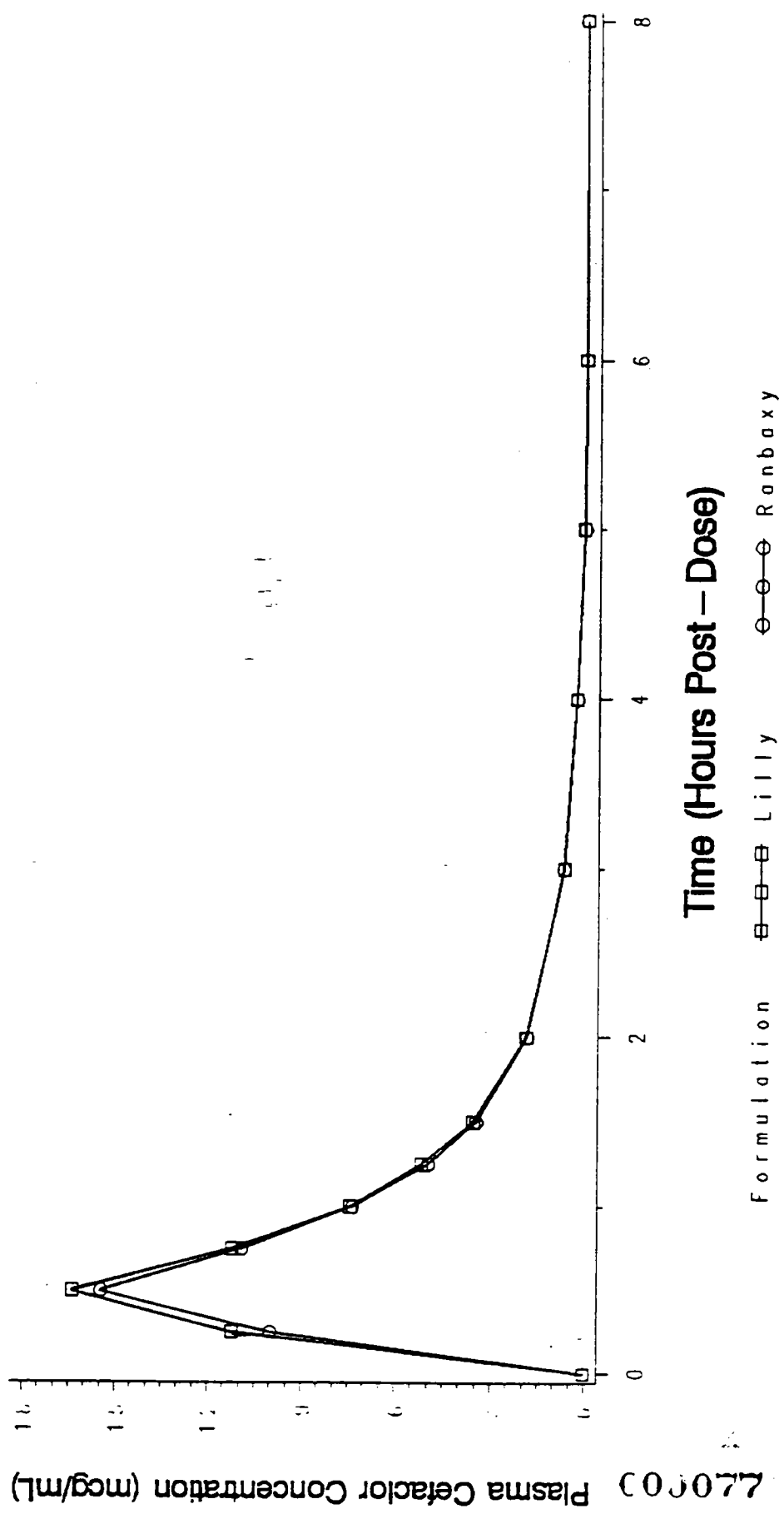
See statistics report for details on calculation of parameters.

Note: AUCinf could not be estimated for Subject No. 17.

Attachment- 2

003071

**Figure 2**  
**Project No. 940784**  
**Mean Plasma Cefaclor Concentrations**  
**(Linear Plot)**



11-02-1995

Table D3

10:38

Project Number :940784  
 Cefaclor in Plasma  
 Pharmacokinetic Parameters by Formulation  
 Formulation: Ranbaxy (A)

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	2									
2	1									
3	2									
4	1									
5	2									
6	2									
7	2									
8	1									
9	2									
10	1									
11	2									
12	1									
13	1									
14	1									
15	2									
16	2									
17	1									
18	1									
19	1									
20	2									
21	1									
22	2									
23	1									
24	2									
Arithmetic Mean		15.81	16.04	98.55	16.4613	0.490	1.1234	0.6240		
± SD		2.375	2.443	0.296	3.42338	0.1560	0.12060	0.06954		
CV%		15.0	15.2	0.3	20.8	31.9	10.7	11.1		
n		24	23	23	24	24	23	23		

Note: AUCinf, kel and t½ could not be estimated for Subject No. 17.

Attachment - 4

G0J083

13-02-1995

Table D4

10:38

Project Number :940784

Cefaclor in Plasma

Pharmacokinetic Parameters by Formulation

Formulation: Lilly (8)

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	1									
2	2									
3	1									
4	2									
5	1									
6	1									
7	1									
8	2									
9	1									
10	2									
11	1									
12	2									
13	2									
14	2									
15	1									
16	1									
17	2									
18	2									
19	2									
20	1									
21	2									
22	1									
23	2									
24	1									
Arithmetic Mean		16.56	16.63	98.39	17.1563	0.500	1.1042	0.6400		
± SD		2.201	2.061	0.486	4.02065	0.1648	0.15181	0.09478		
CV%		13.3	12.4	0.5	23.4	33.0	13.7	14.8		
n		24	23	23	24	24	23	23		

Note: AUCinf, kel and t½ could not be estimated for Subject No. 17.

000084

Attachment-5

15-J2-1995

Table D4  
Project Number :940786  
Cefaclor in Plasma  
Pharmacokinetic Parameters by Formulation  
Formulation: Ranbaxy (fasted) (A)

12:26

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	1	13.4	13.8	97.3	14.599	0.50	1.209	0.573	1.00	3.00
2	3	13.4	13.6	98.3	14.179	0.50	0.979	0.708	1.25	4.00
3	3	14.2	14.5	97.6	15.123	0.50	0.925	0.749	1.25	4.00
4	1	15.5	16.2	95.6	13.523	0.50	0.763	0.909	1.00	4.00
5	2	21.8	22.1	98.6	23.920	0.50	1.093	0.634	1.25	4.00
6	1	15.6	15.9	98.5	15.073	0.50	1.036	0.669	1.25	4.00
7	1	15.5	15.8	98.3	19.165	0.25	0.938	0.739	1.25	4.00
8	1	15.3	15.5	98.6	17.822	0.25	1.012	0.685	1.50	4.00
9	2	15.5	15.7	98.4	15.488	0.50	1.005	0.690	1.25	4.00
10	2	15.2	15.5	97.9	12.107	0.75	1.138	0.609	1.25	4.00
11	2	12.9	13.1	98.5	11.999	0.50	1.042	0.666	1.25	4.00
12	2	13.3	13.6	97.5	15.183	0.50	1.273	0.544	1.00	3.00
13	3	12.5	12.9	97.1	9.160	0.75	1.019	0.681	1.25	4.00
15	3	13.3	13.6	98.0	14.935	0.50	1.014	0.683	1.25	4.00
16	3	16.9	17.3	98.0	17.310	0.25	0.880	0.787	1.50	4.00
17	1	17.4	17.6	98.7	18.156	0.50	0.830	0.835	1.50	5.00
Arithmetic Mean		15.10	15.41	97.93	15.4839	0.484	1.0098	0.6975		
± SD		2.303	2.307	0.789	3.37857	0.1434	0.13101	0.09282		
CV%		15.3	15.0	0.8	21.8	29.6	13.0	13.3		
n		16	16	16	16	16	16	16		

Attachment - 6

000989

15 02-1995

Table D5  
Project Number :940786  
Cefaclor in Plasma  
Pharmacokinetic Parameters by Formulation  
Formulation: Ranbaxy (fed) (B)

12:26

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	3	11.2	11.6	96.6	6.661	0.50	0.947	0.732	1.50	4.00
2	1	12.4	12.9	96.2	10.097	0.25	0.819	0.846	1.25	4.00
3	2	12.2	12.5	97.9	5.347	1.50	0.918	0.755	2.00	5.00
4	2	10.4	10.7	97.0	6.635	0.50	0.772	0.898	1.25	5.00
5	3	20.6	20.8	99.0	10.092	1.00	0.931	0.745	3.00	6.00
6	2	12.9	13.1	98.2	5.657	1.00	0.987	0.702	2.00	5.00
7	3	14.5	14.9	97.3	6.446	0.50	0.829	0.836	2.00	5.00
8	2	13.1	13.3	98.3	6.180	1.50	1.027	0.675	2.00	5.00
9	3	12.8	13.1	97.2	5.632	0.75	0.821	0.844	2.00	5.00
10	3	13.2	13.6	97.5	5.042	1.50	0.884	0.784	2.00	5.00
11	1	13.8	14.1	97.7	9.597	0.50	1.007	0.688	1.25	4.00
12	1	11.0	11.5	95.8	5.773	0.75	0.925	0.750	1.50	4.00
13	2	10.9	11.4	95.4	4.107	1.50	0.711	0.975	2.00	5.00
15	1	12.1	12.4	97.3	6.391	1.00	1.103	0.628	1.50	4.00
16	2	14.0	14.3	98.4	5.572	1.50	0.863	0.803	3.00	6.00
17	3	15.4	15.6	98.2	9.208	0.50	0.884	0.784	1.50	5.00
Arithmetic Mean		13.14	13.48	97.38	6.7773	0.922	0.9018	0.7778		
SD		2.414	2.362	0.996	1.89265	0.4539	0.10082	0.08867		
CV%		18.4	17.5	1.0	27.9	49.2	11.2	11.4		
n		16	16	16	16	16	16	16		

Attachment-7

000990

15-12-1995

Table D6  
Project Number :940786  
Cefaclor In Plasma  
Pharmacokinetic Parameters by Formulation  
Formulation: Lilly (fed) (C)

12:27

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	2	9.6	10.0	96.0	5.761	0.50	0.890	0.779	1.50	4.00
2	2	10.5	11.1	94.2	7.992	0.50	0.704	0.984	1.25	4.00
3	1	13.5	13.9	97.6	7.002	0.50	0.852	0.813	2.00	5.00
4	3	12.8	13.3	96.1	10.302	0.50	0.870	0.797	1.50	4.00
5	1	19.8	20.0	98.9	9.855	0.50	0.852	0.813	3.00	6.00
6	3	11.1	11.9	93.5	6.335	0.50	0.739	0.938	1.50	4.00
7	2	13.6	13.8	98.3	5.122	1.50	0.805	0.861	2.00	6.00
8	3	11.2	11.5	97.6	6.389	0.75	1.126	0.615	1.50	4.00
9	1	14.5	14.8	98.0	6.932	0.50	0.899	0.771	2.00	5.00
10	1	12.4	12.8	97.2	6.122	0.50	0.791	0.876	2.00	5.00
11	3	12.3	12.6	98.1	7.526	0.50	0.855	0.811	1.25	5.00
12	3	10.5	11.0	96.1	5.727	0.75	0.921	0.752	1.50	4.00
13	1	11.5	12.0	95.7	4.467	1.50	0.765	0.906	2.00	5.00
14	2	10.4	10.6	98.0	4.510	1.25	0.938	0.739	2.00	5.00
15	1	15.3	15.7	97.0	7.192	1.50	0.864	0.802	2.00	5.00
16	2	12.6	13.0	97.0	5.229	0.75	0.789	0.879	1.50	5.00
17										
Arithmetic Mean		12.60	13.00	96.83	6.639	0.781	0.8338	0.8211		
± SD		2.480	2.426	1.493	1.68250	0.4070	0.09783	0.08740		
C.V.		19.7	18.7	1.5	25.3	52.1	11.5	10.6		
n		16	16	16	16	16	16	16		

Attachment - 8

000991

**Figure 2**  
**Project No. 940786**  
**Mean Plasma Cefactor Concentrations**  
**(Linear Plot)**

